Associations of Total Protein or Animal Protein Intake and Animal Protein Sources with Risk of Kidney Stones: A Systematic Review and Dose–Response Meta-Analysis

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ABSTRACT

We conducted the present systematic review and meta-analysis to evaluate the association of total protein, animal protein, and animal protein sources with risk of kidney stones in the general population. A literature search was performed in PubMed/Medline, Scopus, and EMBASE up to July 2021. We assessed the credibility of evidence based on NutriGrade scoring system. A total of 14 prospective cohort studies were included. A positive association was observed between higher intake of nondairy animal protein (RR: 1.11; 95% CI: 1.03, 1.20; $I^2 = 0\%$, $n = 4$), total meat and meat products (RR: 1.22; 95% CI: 1.09, 1.38; $I^2 = 13\%$, $n = 3$), and processed meat (RR: 1.29; 95% CI: 1.10, 1.51; $I^2 = 0\%$, $n = 2$) with risk of kidney stones. There was an inverse association between higher intake of dairy protein and risk of kidney stones (RR: 0.91; 95% CI: 0.84, 0.99; $I^2 = 0\%$, $n = 4$). Moreover, each 100-g increment of red meat intake was significantly associated with increased risk of kidney stones (RR: 1.39; 95% CI: 1.13, 1.71). According to the NutriGrade scoring system, the credibility of evidence for most of the exposures was rated as low. We found some kind of publication bias in the association of animal protein intake and risk of kidney stones, according to Egger's and Begg's tests. In the sensitivity analysis of processed meat as well as dairy consumption with risk of kidney stones we observed in each individual analysis, 1 study changed the overall estimate. Further observational studies are needed to confirm the present results. The protocol of the present study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021230125: https://www.crd.york.ac.uk/PROSPERO). *Adv Nutr* 2022;13:821–832.

Statement of Significance: In the present study, we found a positive association between dietary intake of nondairy animal protein, total meat and meat products, and red meat and processed meat with risk of kidney stones, whereas a negative association was observed between dairy protein and risk of kidney stones.

Keywords: kidney stones, animal protein, fish, meat, dairy, poultry, nutrition, meta-analysis, systematic review

Introduction

Kidney stones, also known as nephrolithiasis, are a common, painful urologic disorder. Incidence of kidney stones is increasing worldwide, with up to 12% of the world population having experienced kidney stones in their lives (1, 2). Kidney stones are associated with an increased risk of systemic diseases, including cardiovascular events (3), bone fractures (4), chronic kidney diseases (5), renal cell carcinoma (6), end-stage renal disease, and mortality (7). Given the substantial cost of kidney stone disease imposed on the health care system (8), it is essential to find appropriate approaches to prevent kidney stone formation. In this regard, environmental factors like lifestyle and nutrition considerations could be effective intervention targets (9). Since protein-rich food consumption is a crucial factor in the pathogenesis of nephrolithiasis, some researchers have focused on dietary protein intake and its correlation with the incidence of kidney stones (10). Ingested protein as a rich

source of purine, producing an acid load, increases urinary calcium and oxalate excretion, and seems to be involved in raising the risk of kidney stones (11, 12). Also, the high content of amino acids containing sulfur in dietary animal protein results in lower urinary pH and citrate, which has been found to be associated with kidney stones (13). At the same time, dairy animal protein by a positive calcium balance and binding with excess oxalate in the intestine may reduce the risk of calcium stone formation (10). Hence, the overall effect of each protein source on renal stone disease has not been completely clarified.

Several previous cohort studies have reported that animal protein was positively associated with kidney stone formation (14, 15), while other studies reported no such association (16, 17). A prospective cohort study conducted in the UK Biobank reported that greater meat intake (50 g increase in meat/wk) is associated with a 17% increased risk of kidney stones (18). In contrast, no significant association between meat consumption and risk of stone formation was observed in the results of the Seguimiento Universidad de Navarra (SUN) cohort (19). However, protective effects of dairy protein for kidney stone risk have been shown in the Nurses' Health Study II but not in the Nurses' Health Study I and the Health Professionals Follow-Up Study (20). Accordingly, the association between the amount or type of dietary protein intake and the risk of kidney stones is inconsistent.

The previous study reviewed the literature about multivariate dietary risk factors for nephrolithiasis (10). In addition, in the meta-analysis of Lin et al. (21), the authors examined only the relation between total meat consumption as well as animal protein intake with risk of kidney stones, but its procedure was less powerful in that it included a study with a case-control design (22). However, the dose–response associations between specific types of dietary protein and the risk of kidney stones in none of these studies have been investigated. Consequently, there is currently no study that has quantitatively synthesized the available evidence in this regard. Hence, we conducted a systematic review and dose–response meta-analysis of prospective cohort studies to evaluate the association between total protein, animal protein, and animal protein sources with the risk of kidney stones.

Methods

This systematic review and meta-analysis was designed, conducted, and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (23). The protocol of this study has been registered at PROSPERO (CRD42021230125: https://www.crd.york.ac. uk/PROSPERO).

Search strategy

We performed a systematic search of online databases including MEDLINE (via PubMed), Embase (via Ovid), Scopus, and Google Scholar until July 2021 to identify observational studies that examined the association between

total protein, animal protein intake, and animal protein sources and the risk of kidney stones. The details of the search strategy are shown in **Supplemental Table 1**. No restrictions in terms of language or publication time were considered. We also checked the reference lists of relevant publications manually to identify additional studies.

Study selection: inclusion and exclusion criteria

We included published prospective observational studies if they met following criteria: 1) conducted in adults (≥18 y old); 2) considered the intake of total protein, animal protein (protein derived from pork, beef, lamb, fish, seafood, poultry, egg, animal liver, organ meat, milk), and animal protein sources (red meat, total meat and meat products, processed meat, poultry, fish, and dairy) as the exposure variable, and the risk of kidney stones as the outcome variable; 3) reported HRs, risk ratio, RRs, or ORs with 95% CIs for the association between total protein, animal protein, and animal protein sources and risk of kidney stones. For findings from 1 dataset that were published in >1 article, we included the most recent version with the greatest number of participants. We excluded letters, comments, reviews, meta-analyses, and animal and ecological studies. Studies conducted in children or adolescents and studies with insufficient data were also excluded.

Data extraction

Two independent investigators (FA, ST) extracted the required data from each of the eligible studies and any disagreements were resolved by discussion with the principal investigator (HM). The following information was extracted from each eligible article: first author's name, publication year, country of origin, participant's age range or mean age, sex, duration of follow-up, number of participants and cases, methods used for the assessment of total protein, animal protein and animal protein sources, the categories of exposure, any reported effect estimates with corresponding 95% CIs, and covariates adjusted in the statistical analysis.

Statistical analysis

Risk ratios were considered as the primary endpoint in this meta-analysis. The reported HRs and risk ratios in each included studies were considered as equal to RRs (24). Given the very low incidence rate (<5%), the reported ORs were considered equal to RRs (25).

Meta-analyses were performed according to total protein, animal protein, nondairy animal protein, dairy protein, total meat and meat products, red meat, processed meat, poultry, fish, whole milk, and skim milk, as a separate exposure. For the main analyses, we pooled the RRs comparing the highest with the lowest categories of dietary exposures. A fixed-effects model was performed when the number of studies in each individual analysis was <5; otherwise, we used a random-effects model (26). In both fixed-effects and random-effects models, maximally adjusted RRs were

used. Between-studies heterogeneity was evaluated with the Q-statistic and the I^2 values, and results were considered heterogeneous if $I^2 > 50\%$ [27]. To discover the potential sources of heterogeneity in analyses that included more than 5 studies, we performed subgroup analyses based on main confounders. Publication bias was assessed using the Egger's regression asymmetry test [28] and Begg's test [29]. The trim-and-fill method was used to determine the effect of any publication on the overall effect [30]. To examine the influence of each study on pooled RR, sensitivity analysis was conducted in which each study was omitted in each step.

To calculate the RRs per unit increase in dietary exposures, we used the method suggested by Greenland and Longnecker [31] and Orsini et al. [32]. This method requires the distributions of cases, sample size, and the RRs across ≥ 3 categories of exposures. Study-specific results were combined by using a random-effects model when the number of studies was more than 5. The median point in each category of exposure was considered as the corresponding dose. If the exposure was reported as a range, we calculated approximate mean of the lower and upper boundaries. When the extreme categories were open-ended, the amplitude of these open-ended intervals was expected to be the same as the closest category.

A 1-stage, weighted, mixed-effects meta-analysis was used to clarify the shape of the dose–response associations [33]. If restricted cubic splines could not be calculated due to the limited number of observations, we used the best-fitting second-order fractional polynomial curve to the data [33]. Statistical analyses were conducted using STATA version 14.0 (StataCorp). $P < 0.05$ was considered statistically significant for all tests, including Cochran's Q test.

Quality assessment
We performed a quality bias assessment of included studies using the Newcastle–Ottawa Scale (NOS) [34]. The NOS total score ranged from 0 to 9 points, whereby a higher score indicates higher study quality. NOS scores of ≥ 7 were identified as high-quality studies.

Credibility of evidence assessment
We evaluated the credibility of evidence for the association between different types of exposures and risk of kidney stones by using the NutriGrade scoring system [35]. NutriGrade consists of the following criteria for meta-analyses of prospective studies: *1)* risk of bias (up to 2 points), *2)* precision (up to 1 point), *3)* heterogeneity (up to 1 point), *4)* directness (up to 1 point), *5)* publication bias (up to 1 point), *6)* funding bias (up to 1 point), *7)* effect sizes (up to 2 points), and *8)* dose–response (up to 1 point) [35]. According to this scoring system, 4 categories were recommended to interpret the certainty of meta-analysis evidence: high (≥ 8 to 10 points), moderate (6 to 7.99 points), low (4 to 5.99 points), and very low (0 to <4 points).

Results

Characteristics of included studies
A total of 1782 records from the 3 databases were included by our systematic literature search. After removing the 695 duplicate records, 1087 records were screened for the titles and abstracts based on the inclusion criteria. After exclusion of 1059 records, 28 studies were further assessed for eligibility. After the full-text review, 14 studies were excluded (**Supplemental Table 2**). Finally, we included 14 studies in the final analysis (14, 16, 18–20, 36–43) (**Figure 1**).

Table 1 shows the characteristics of the included prospective cohort studies. The included studies were conducted in the United States ($n = 9$), United Kingdom ($n = 2$), Spain ($n = 1$), China ($n = 1$), and Finland ($n = 1$). The number of participants in these studies ranged from 16,094 to 439,072 and the number of cases ranged from 303 to 4462. In total, 1,680,291 subjects and 30,417 cases were included in the eligible studies. For exposure measurement, 13 studies had used a food-frequency questionnaire (FFQ) and only 1 study had used a diet questionnaire. Most studies controlled for some conventional risk factors, including age ($n = 11$), BMI ($n = 10$), and calcium supplementation ($n = 10$).

Total protein consumption and risk of kidney stones
Two studies examined the association between intake of total protein and kidney stones (14, 41). Total protein intake was not associated with risk of kidney stones. The pooled RR for the highest intake compared with the lowest intake was 1.04 (95% CI: 0.92, 1.18; **Supplemental Figure 1**); however, moderate heterogeneity between studies was found ($I^2 = 67.7\%$, $P = 0.07$) (**Table 2**). The pooled RRs for a 10-g increment of total protein intake was 0.99 (95% CI: 0.98, 1.01; **Supplemental Figure 2**) (**Table 2**). Total protein consumption was not nonlinearly associated with risk of kidney stones ($P = 0.11$ for nonlinearity; **Supplemental Figure 3**).

Animal protein consumption and risk of kidney stones
Six studies examined the association between animal protein intake and kidney stones (14, 16, 17, 36, 38, 41). Animal protein intake was not associated with risk of kidney stones. The pooled RR for the highest intake of animal protein compared with the lowest intake was 1.00 (95% CI: 0.89–1.14; **Supplemental Figure 4**); there was a moderate heterogeneity between studies ($I^2 = 61.7\%$, $P = 0.02$) (**Table 2**). Based on 5 studies in the linear dose–response meta-analysis (14, 16, 36, 38, 41), we found no significant association between animal protein intake and risk of kidney stones by an additional 10 g/d of animal protein (RR: 0.99; 95% CI: 0.97, 1.02; **Supplemental Figure 5**) (**Table 2**). Animal protein consumption was not nonlinearly associated with risk of kidney stones ($P = 0.26$ for nonlinearity; **Supplemental Figure 6**). In the subgroup analyses based on a fixed-effects model, there were no associations across subgroups based on sex, age, follow-up duration, and adjustment for BMI, calcium supplementation, alcohol consumption, and fluid intake (**Table 3**).
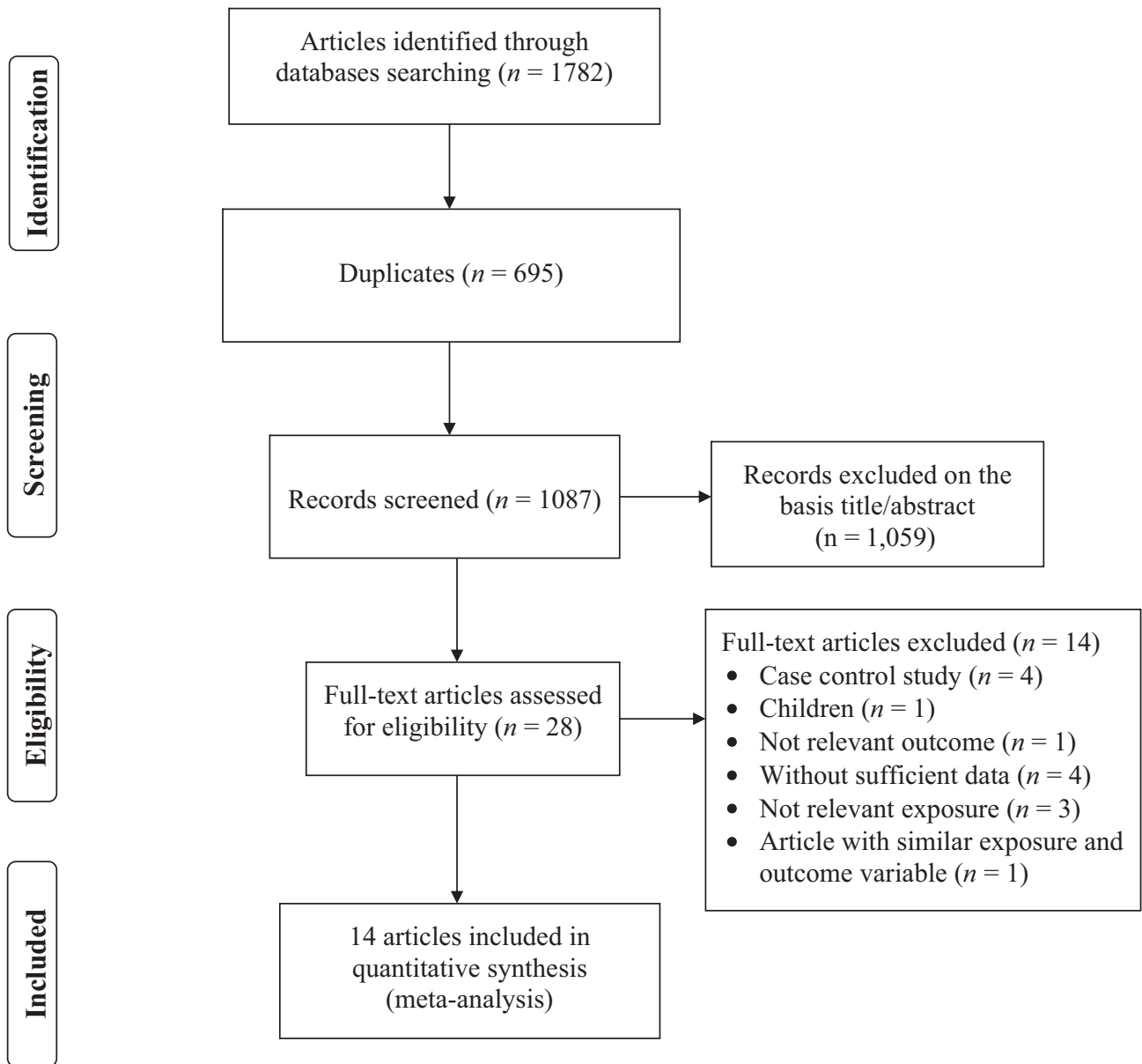
FIGURE 1 Literature search and review flow diagram for selection of studies.

Nondairy animal protein consumption and risk of kidney stones

The overall RR from 2 studies (14, 20) indicated a significant positive association between nondairy animal protein intake and risk of kidney stones (RR: 1.11; 95% CI: 1.03, 1.20; **Supplemental Figure 7**), with no significant between-studies heterogeneity ($I^2 = 0.0\%$, $P = 0.46$) (Table 2). In linear dose–response meta-analysis, we found no significant association between a 10-g/d increment of nondairy animal protein intake and risk of kidney stones (RR: 1.01; 95% CI: 1.00, 1.02; **Supplemental Figure 8**) (Table 2). Nondairy animal protein consumption was not nonlinearly associated with risk of kidney stones ($P = 0.38$ for nonlinearity; **Supplemental Figure 9**).

Dairy protein consumption and risk of kidney stones

Two studies revealed the association between dairy protein intake and risk of kidney stones (14, 20). Pooling 4 RRs from these studies indicated an inverse significant association between dairy protein intake and risk of kidney stones (RR: 0.91; 95% CI: 0.84, 0.99; **Supplemental Figure 10**) and no significant between-studies heterogeneity was found ($I^2 = 0.0\%$, $P = 0.54$) (Table 2). Linear dose–response analysis showed that a 10-g increase in the dairy protein was weakly associated with a decreased risk of kidney stones (RR: 0.96; 95% CI: 0.93, 0.99; **Supplemental Figure 11**) (Table 2). Dairy protein consumption was not nonlinearly associated with risk of kidney stones ($P = 0.86$ for nonlinearity; **Supplemental Figure 12**).

TABLE 1 Characteristics of included studies in the systematic review and meta-analysis evaluating the association between total protein, animal protein, and animal protein sources with the risk of kidney stones[1]

First author (year, country) (reference)	Research study	Age (y), sex	Follow-up, y	Cases/cohort size, n/n	Exposure assessment (items)	Outcome assessment	Exposure type	Comparison	RR (95% CI): highest vs. lowest	Covariate[2]
Littlejohns et al. (2020, UK) (18)	UK Biobank	40–69, Both	6	2057/439,072	Short FFQ	Clinical record	Total meat and meat product	Q5 vs. Q1	1.21 (1.05–1.39)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 24
							Red meat	Q5 vs. Q1	1.20 (1.04–1.38)	
							Processed meat	Q5 vs. Q1	1.32 (1.12–1.59)	
							Poultry	Q5 vs. Q1	0.99 (1.04–1.38)	
							Fish	Q4 vs. Q1	1.03 (0.87–1.22)	
Rodriguez et al. (2020, USA) (42)	HPFS	40–75, Male	26	1963/42,902	FFQ	Self-report, medical record	Red meat	Unclear	1.02 (0.93–1.12)	1, 5, 7, 8, 16, 17, 24, 25, 27, 28
							Fish		1.03 (0.93–1.12)	
	NHS I	30–55, Female	20	1599/59,994			Red meat		0.88 (0.80–0.97)	
							Fish		1.03 (0.93–1.14)	
	NHS II	25–42, Female	20	3014/90,631			Red meat		0.92 (0.85–0.98)	
							Fish		1.02 (0.94–1.09)	
Shu et al. (2019, China) (14)	SWHS and SMHS	40–70, Both	8	2653/127,220	FFQ, Chinese food-composition table	Recall	Animal protein	Q5 vs. Q1	1.16 (1.01–1.32)	3, 5, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
							Nondairy animal protein	Q5 vs. Q1	1.14 (1.01–1.30)	
							Dairy protein	Q5 vs. Q1	0.96 (0.84–1.10)	
							Total protein	Q5 vs. Q1	1.09 (0.95–1.25)	
Leone et al. (2017, Spain) (19)	SUN	50–64, Both	9.6	735/16,094	FFQ (136)	Self-report Physician	Total meat and meat product	Q5 vs. Q1	1.13 (0.87–1.46)	1, 2, 3, 5, 8, 9, 11, 16, 17, 21, 22, 23, 24, 25, 26
							Fish	Q5 vs. Q1	1.00 (0.80–1.26)	
Ferraro et al. (2016, USA) (20)	HPFS	≤70, Male	26	1963/42,919	FFQ	Self-report, medical record	Nondairy animal protein	Q5 vs. Q1	1.15 (0.97–1.36)	1, 5, 6, 8, 16, 17, 24, 28, 29, 30, 31, 32, 33, 34
							Dairy protein	Q5 vs. Q1	0.93 (0.78–1.10)	
	NHS I	≤65, Female	20	1331/60,128			Nondairy animal protein	Q5 vs. Q1	1.20 (0.99–1.46)	
							Dairy protein	Q5 vs. Q1	0.95 (0.76–1.17)	
	NHS II	≤55, Female	20	3024/90,629			Nondairy animal protein	Q5 vs. Q1	1.02 (0.90–1.17)	
							Dairy protein	Q5 vs. Q1	0.84 (0.73–0.96)	
Turney et al. (2014, UK) (43)	EPIC-Oxford	≥20, Both	20	303/51,336	FFQ	Self-report, hospital record	Total meat and meat product	T3 vs. T1	1.64 (1.08–2.48)	5, 6, 9, 16, 23
							Red meat	T3 vs. T1	1.53 (1.04–2.26)	
							Processed meat	T3 vs. T1	1.13 (0.76–1.67)	
							Poultry	T3 vs. T1	1.35 (0.95–1.93)	
Ferraro et al. (2013, USA) (40)	HPFS and NHS I and NHS II	25–75, Both	10.5	4462/194,095	FFQ	Self-report, medical record	Whole milk	Q5 vs. Q1	0.99 (0.82–1.19)	1, 4, 5, 8, 16, 17, 19, 23, 27, 28, 30, 33, 34, 35, 36, 37, 38
							Skim milk	Q5 vs. Q1	0.91 (0.82–1.01)	

(Continued)

TABLE 1 (*Continued*)

First author (year, country) (reference)	Research study	Age (y), sex	Follow-up, y	Cases/cohort size, n/n	Exposure assessment (items)	Outcome assessment	Exposure type	Comparison	RR (95% CI): highest vs. lowest	Covariate[2]
Sorensen et al. (2012, USA) (17)	WHI OS	50–79, Female	8	1952/78,293	FFQ	Self-reported	Animal protein	Q5 vs. Q1	1.11 (0.96–1.28)	Unadjusted
Taylor et al. (2004, USA) (16)	HPFS	40–75, Male	14	1473/45,619	Semi-FFQ (131)	Self-report, medical record	Animal protein	Q5 vs. Q1	1.01 (0.86–1.19)	1, 5, 6, 8, 19, 24, 27, 28, 29, 30, 34, 39
Curhan et al. (2004, USA) (36)	NHS II	27–44, Female	8	1223/96,245	Semi-FFQ (131)	Self-report, medical record	Animal protein	Q5 vs. Q1	0.84 (0.68–1.04)	1, 5, 8, 19, 24, 29, 30, 33, 34, 40, 41
Hirvonen et al. (1999, Finland) (41)	ATBC	50–69, Male	6.1	329/27,001	Diet questionnaire (276)	Physician diagnosed	Animal protein / Total protein / Whole milk / Skim milk	NR	0.69 (0.49–0.97) / 0.78 (0.55–1.10) / 1.00 (1.94–1.08) / 1.00 (1.94–1.07)	1, 6, 21, 39, 43, 44, 45
Curhan et al. (1998, USA) (39)	NHS	30–55, Female	8	719/81,093	Semi-FFQ (131)	Self-report, medical record	Whole milk / Skim milk	NR	0.90 (0.71–1.15) / 0.98 (0.86–1.12)	1, 8, 19, 29, 30, 34, 37, 40
Curhan et al. (1997, USA) (38)	NHS I	30–55, Female	12	864/91,731	Semi-FFQ (131)	Self-report, medical record	Animal protein	Q5 vs. Q1	0.99 (0.78–1.28)	1, 5, 6, 8, 19, 24, 29, 30, 34, 40
Curhan et al. (1996, USA) (37)	HPFS	40–75, Male	6	753/45,289	Semi-FFQ (131)	Self-report, medical record	Whole milk / Skim milk	NR	0.87 (0.71–1.05) / 0.97 (0.85–1.10)	1, 4, 19, 28, 30, 34, 37, 42

[1] ATBC, The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study; EPIC-Oxford, Oxford arm of the European Prospective Investigation into Cancer and Nutrition; FFQ, food-frequency questionnaires; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II; NR, not reported; Q, quintile; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; SUN, Seguimiento Universidad de Navarra Follow-up; T, tertile; WHI OS, Women's Health Initiative Observational Study.

[2] Covariate: age (1), sex (2), education (3), ethnicity (4), BMI (5), alcohol consumption (6), coffee (7), calcium supplementation (8), smoking (9), Townsend deprivation score (10), physical activity (11), birth year (12), income (13), waist-hip ratio (14), history of coronary artery disease/stroke (15), history of type 2 diabetes (16), history of hypertension (17), and history of cholelithiasis (18), dietary calcium intake (19), dietary oxalate intake (20), marital status (21), time spent watching television (22), total energy intake (23), total water intake (24), vitamin D supplementation (25), year of recruitment (26), supplemental vitamin C (27), use of thiazides (28), sodium (29), potassium (30), fructose (31), oxalate (32), phytate (33), all sources of protein (34), race (35), use of furosemide (36), all the beverages (37), gout (38), magnesium intake (39), sucrose (40), family history of kidney stones (41), profession (42), vocational training (43), fiber (44), and supplementation group (45).

TABLE 2 Summary risk estimates for the highest compared with lowest category and dose–response meta-analysis of the association between animal protein sources and risk of kidney stones

Exposure	Highest vs. lowest category meta-analysis				Dose–response meta-analysis				
	Studies, n	RR (95% CI)	I^2, %	P^1	Studies, n	Dose unit, g/d	RR (95% CI)	I^2, %	P^1
Animal protein	6	1.00 (0.89–1.14)	61.7	0.02	5	10	0.99 (0.97–1.02)	71.7	0.00
Red meat	5	1.02 (0.91–1.15)	81.1	0.00	5	100	1.39 (1.13–1.71)	0.0	0.35
Fish	5	1.02 (0.98–1.07)	0.0	0.99	5	100	0.98 (0.86–1.11)	0.0	0.95
Nondairy animal protein	4	1.11 (1.03–1.20)	0.0	0.46	4	10	1.01 (1.00–1.02)	41.8	0.16
Dairy protein	4	0.91 (0.84–0.99)	0.0	0.54	4	10	0.96 (0.93–0.99)	0.0	0.56
Whole milk	4	0.97 (0.90–1.04)	0.0	0.58	4	200	0.97 (0.91–1.03)	0.0	0.58
Skim milk	4	0.96 (0.91–1.02)	0.0	0.61	4	200	0.96 (0.92–1.01)	0.0	0.58
Total meat and meat products	3	1.22 (1.09–1.38)	12.8	0.31	3	100	1.13 (1.05–1.22)	83.1	0.0
Poultry	2	1.12 (0.90–1.40)	43.4	0.18	2	100	1.72 (1.45–2.04)	0.0	0.75
Processed meat	2	1.29 (1.10–1.51)	0.0	0.48	2	50	1.18 (0.94–1.48)	0.0	0.98
Total protein	2	1.04 (0.92–1.18)	67.7	0.07	2	10	0.99 (0.98–1.01)	44.7	0.17

$^1 P < 0.05$ is statistically significant.

Total meat, meat product consumption, and risk of kidney stones

Considering 3 RRs from studies that examined association between intake of total meat, meat products, and risk of kidney stones (18, 19, 43), we found a positive association between total meat, meat products, and risk of kidney stones (RR: 1.22; 95% CI: 1.09, 1.38; **Supplemental Figure 13**), with no significant between-studies heterogeneity ($I^2 = 12.8\%$, $P = 0.31$) (Table 2). The pooled RR was 1.13 (95% CI: 1.05, 1.22) (**Supplemental Figure 14**) for a 100-g increment of total meat and meat product intake (Table 2). Nonlinear dose–response meta-analysis showed that an increased intake of total meat and meat products to 100 g/d was associated with a sharp and significant increase in the risk of kidney stones. After that, increasing intake of total meat and meat products had a slight positive association with the risk of kidney stones ($P = 0.05$ for nonlinearity; **Figure 2**A).

Red meat consumption and risk of kidney stones

Pooled analysis of 5 RRs from 3 studies (18, 42, 43) revealed no association between red meat consumption and risk of kidney stones (RR: 1.02; 95% CI: 1.09, 1.15; **Supplemental Figure 15**), with substantial heterogeneity between studies ($I^2 = 81.1\%$, $P < 0.001$) (Table 2). Linear dose–response meta-analysis on 2 eligible studies (18, 43) showed a significant positive association between a 100-g increase in red meat intake and risk of kidney stones (RR: 1.39; 95% CI: 1.13, 1.71; **Supplemental Figure 16**) (Table 2). Red meat consumption and risk of kidney stones were not nonlinearly associated, but the risk of kidney stones significantly increased in linear fashion ($P = 0.91$ for nonlinearity; Figure 2B). We performed subgroup analyses based on a fixed-effects model to find sources of heterogeneity. In the subgroup analyses, we found that sex, follow-up duration, and adjustment for fluid intake and alcohol consumption might explain between-study heterogeneity (Table 3).

Processed-meat consumption and risk of kidney stones

Two studies reported results regarding the association between processed-meat intake and risk of kidney stones (18, 43). The pooled RR for the highest intake versus lowest intake was 1.29 (95% CI: 1.10, 1.51) (**Supplemental Figure 17**), with no significant heterogeneity between studies ($I^2 = 0.0\%$, $P = 0.48$) (Table 2). We found no significant association in linear dose–response meta-analysis for a 50-g/d increment of processed meat (RR: 1.18, 95% CI: 0.94, 1.48; **Supplemental Figure 18**) (Table 2). Processed-meat consumption was not nonlinearly associated with risk of kidney stones ($P = 0.19$ for nonlinearity; **Supplemental Figure 19**).

Poultry consumption and risk of kidney stones

Pooled RRs of 2 studies regarding the association between poultry intake and risk of kidney stones (18, 43) showed no statistically significant association with the risk of kidney stones (RR: 1.12; 95% CI: 0.90, 1.40; **Supplemental Figure 20**) (Table 2). Moderate heterogeneity between studies was found ($I^2 = 43.4\%$, $P = 0.18$) (Table 2). Linear dose–response meta-analysis showed that each additional 100 g/d of poultry intake was associated with an increased risk of kidney stones by 72% (RR: 1.72, 95% CI: 1.45, 2.04; **Supplemental Figure 21**) (Table 2). In the nonlinear dose–response meta-analysis, we found that poultry consumption was not nonlinearly associated with risk of kidney stones ($P = 0.11$ for nonlinearity; Figure 2C).

Fish consumption and risk of kidney stones

Pooled analysis of 3 studies with 5 RRs (18, 19, 42) indicated no statistically significant association between fish intake and risk of kidney stones (RR: 1.02; 95% CI: 0.98, 1.07; **Supplemental Figure 22**) (Table 2). Also, no evidence of statistically significant between-study heterogeneity was found ($I^2 = 0.0\%$, $P = 0.99$) (Table 2). Linear dose–response meta-analysis on 2 studies (18, 19) yielded a null association

TABLE 3 Subgroup analyses for animal protein intake and red meat intake with the risk of kidney stones

Variables	Effect sizes, n	Q test	RR (95% CI)[1]	I², [2] P-heterogeneity[3]	P-between[4]
Animal protein, overall	6	13.06	1.00 (0.89, 1.14)	61.7, 0.02	
Sex					0.14
Men	2	5.24	0.89 (0.57, 1.37)	80.9, 0.02	
Women	3	4.57	0.99 (0.83, 1.17)	56.2, 0.10	
Both	1	0	1.17 (1.03, 1.33)	0	
Follow-up duration (y)					0.94
<10	4	13.36	0.97 (0.80, 1.18)	77.5, 0.004	
≥10	2	0.32	1.05 (0.91, 1.21)	0.0, 0.57	
Mean age (y)					0.92
<55	3	7.19	1.00 (0.81, 1.24)	72.2, 0.02	
≥55	3	6.48	0.99 (0.80, 1.22)	69.1, 0.03	
Adjusted for BMI					0.72
Yes	4	7.23	1.03 (0.89, 1.19)	58.5, 0.06	
No	2	6.33	0.90 (0.57, 1.43)	84.2, 0.01	
Adjusted for fluid intake					0.12
Yes	3	3.22	0.97 (0.83, 1.13)	37.9, 0.20	
No	3	8.08	1.03 (0.83, 1.26)	75.2, 0.01	
Adjusted for alcohol intake					0.23
Yes	3	5.25	0.94 (0.74, 1.18)	61.9, 0.07	
No	3	7.01	1.05 (0.88, 1.24)	71.5, 0.03	
Adjusted for calcium supplementation					0.72
Yes	4	7.23	1.03 (0.89, 1.19)	58.5, 0.06	
No	2	6.33	0.90 (0.57, 1.43)	84.2, 0.01	
Red meat, overall	5	21.15	1.02 (0.91, 1.15)	81.1, <0.001	
Sex					<0.001
Men	1	0	1.02 (0.93, 1.12)	—	
Women	2	0.53	0.91 (0.86, 0.96)	0.0, 0.46	
Both	2	1.33	1.23 (1.08, 1.41)	24.8, 0.24	
Follow-up duration (y)					0.002
<10	1	0	1.20 (1.04, 1.38)	—	
≥10	4	11.15	0.94 (0.90, 0.99)	73.1, 0.01	
Mean age (y)					0.20
<55	4	19.48	0.95 (0.90, 1.00)	84.6, <0.001	
≥55	1	0	1.02 (0.93, 1.12)	—	
Adjusted for fluid intake					<0.001
Yes	3	5.08	0.94 (0.89, 0.98)	60.7, 0.08	
No	2	1.33	1.23 (1.08, 1.41)	24.8, 0.25	
Adjusted for alcohol intake					<0.001
Yes	2	1.33	1.23 (1.08, 1.41)	24.8, 0.25	
No	3	5.08	0.94 (0.89, 0.98)	60.7, 0.08	
Adjusted for calcium supplementation					0.72
Yes	4	15.70	0.96 (0.92, 1.01)	80.9, <0.01	
No	1	0	1.53 (1.04, 2.26)	—	

[1]Obtained from the random-effects model.
[2]Inconsistency, percentage of variation across studies due to heterogeneity.
[3]Obtained from the Q test.
[4]Heterogeneity between groups ($P < 0.05$ is statistically significant).

between a 100-g increment of fish intake and risk of kidney stones (RR: 0.98, 95% CI: 0.86, 1.11; **Supplemental Figure 23**) (Table 2). Fish consumption was not nonlinearly associated with risk of kidney stones ($P = 0.36$ for nonlinearity; **Supplemental Figure 24**).

Milk consumption and risk of kidney stones
Four studies reported risk estimates for milk intake (37, 39–41), but separately for skim milk and whole milk. With regard to whole milk, the overall RR from 4 studies showed a nonsignificant association for risk of kidney stones (RR: 0.97; 95% CI: 0.90, 1.04; **Supplemental Figure 25**) (Table 2). A similar nonsignificant association was found in linear dose–response meta-analysis of these studies between a 200-g/d increase in whole-milk intake and risk of kidney stones (RR: 0.97; 95% CI: 0.91, 1.03; **Supplemental Figure 26**) (Table 2). The pooled RR for the highest intake compared with the lowest intake of skim milk was 0.96 (95% CI: 0.91, 1.02) (Table 2) (**Supplemental Figure 27**). Linear dose–response meta-analysis showed no significant association between a 200-g/d increase in skim-milk intake and risk of kidney
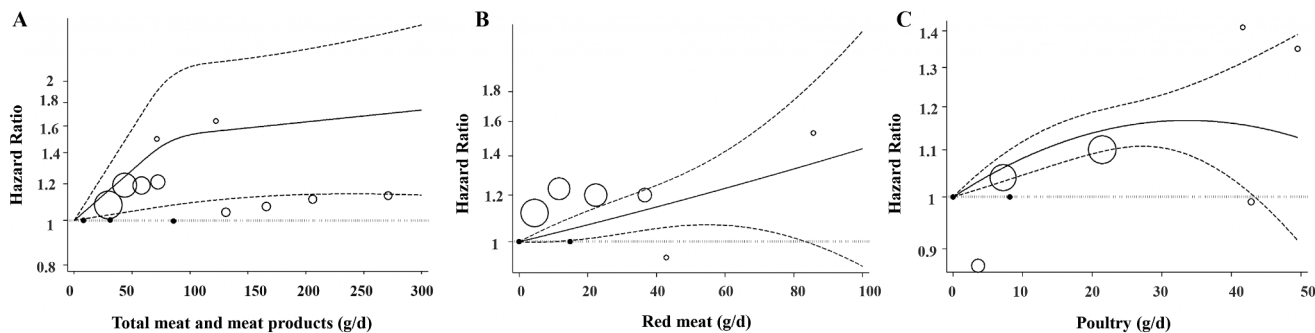
FIGURE 2 Nonlinear dose–response association of total meat and meat product intake (A), red meat intake (B), and poultry intake (C) and risk of kidney stones. Modeling was performed using restricted cubic splines with knots fixed at the 10th, 50th, and 90th percentiles of the distribution. The solid line represents nonlinear dose response and dotted lines represent 95% CIs. Circles represent HR point estimates for categories of total meat and meat product intake (A), red meat intake (B), and (C) poultry intake from each study, with circle size proportional to the inverse of standard error. Small solid circles represent baseline category of total meat and meat product intake (A), red meat intake (B), and (C) poultry intake for each separate study.

stones (RR: 0.96; 95% CI: 0.92, 1.01; **Supplemental Figure 28**) (Table 2).

Sensitivity analyses and publication bias
Sensitivity analysis for the association between processed meat and risk of kidney stones showed that the exclusion of the study by Littlejohns et al. (18) changes the significant positive association between processed-meat intake and risk of kidney stones to a nonsignificant association (RR: 1.13; 95% CI: 0.76, 1.67). Similar results were seen with regard to nondairy animal protein when the study by Shu et al. (15) was excluded (RR: 1.09; 95% CI: 0.99, 1.20). In the sensitivity analysis for the association between dairy protein and risk of kidney stones, removing the study of Ferraro et al. (20). (NHS II) changed the significant inverse association to a nonsignificant association (RR: 0.94; 95% CI: 0.86, 1.04). For the other associations, removal of any single study from the analysis did not substantially alter the pooled RR. After assessing publication bias based on Begg's and Egger's linear correlation test, we found that there is possible publication bias in the association of animal protein intake and risk of kidney stones ($P = 0.02$ Begg's test and $P = 0.01$ Egger's test). However, adjustment with the use of the trim-and-fill method did not result in a change in the average RR (RR: 1.00; 95% CI: 0.88, 1.14; $n = 6$ studies).

Study quality and credibility assessment
The majority of included studies were high quality based on NOS criteria (**Supplemental Table 3**). The credibility of evidence for 9 exposures was low based on the NutriGrade tool (**Supplemental Table 4**). With regard to nondairy animal protein and total meat and meat products, credibility of evidence was very low and moderate, respectively.

Discussion
We found a positive significant association between nondairy animal protein, total meat and meat products, red meat,

and processed meat with risk of kidney stones, but with regard to dairy protein, a significant negative association was observed. There was no significant association between total protein, animal protein, poultry, fish, whole-milk, and skim-milk consumption and incidence of kidney stones. Dose–response meta-analysis indicated that each 100-g/d increase in total meat and meat products, red meat, and poultry was associated with a 13%, 39%, and 72% lower risk of kidney stones, respectively.

Total protein
There was no association between total protein intake and risk of kidney stones in our study. In contrast to our finding, a cross-sectional study showed that total protein intake had a positive correlation with greater urine calcium, urine sulfate, and uric acid excretions and an increased risk of kidney stones (44). Also, Wasserstein et al. reported that a high dietary protein intake increased the risk of recurrent stone formation and that these individuals were more sensitive to the calciuric effect of dietary protein (45). Some studies found that individuals who follow a low-protein diet rich in vegetables and fruits had a lower prevalence of kidney stones (10, 46). Furthermore, a clinical trial study reported that moderate dietary protein restriction in patients with idiopathic hypercalciuria and calcium nephrolithiasis resulted in decreases in urinary calcium, uric acid, oxalate, and hydroxyproline but increases in urinary citrate (47). Dietary protein could increase the risk of kidney stones by various mechanisms. Increased production of acids in the body is the main mechanism that might stimulate bone resorption and higher excretion of urinary calcium (48, 49). Also, this mild acidosis may increase urinary net acid excretion that, in turn, prevents calcium reabsorption and consequently results in an increased risk of kidney stones (50, 51). Due to the hypercalciuric effect of dietary protein, this may increase urinary sulfate excretion, which may result in calcium-sulfate complex formation in the renal tubules that are poorly

absorbable (51). Furthermore, the acidic properties of dietary protein can result in hypocitraturia, which is another risk factor for nephrolithiasis (51–53). Increased intake of dietary protein, which is a rich source of purine, increases urinary excretion of uric acid (54). Hyperuricosuria manifests as pure uric acid stones and recurrent calcium oxalate stones (55, 56). Previous studies have indicated the beneficial effects of a balanced vegetarian diet with low-fat dairy products on kidney stone patients (10). Adherence to these dietary patterns due to higher consumption of fruits and vegetables and lower meat consumption results in a lower potential renal acid load (PRAL), which could decrease net endogenous acid production (NEAP) and, consequently, risk of kidney stone formation (57).

Animal protein
Animal protein consists of nondairy animal protein (red meat, poultry, fish) and dairy animal protein. Nondairy animal protein was associated with increased risk of kidney stones in our study. Elevated dietary amount of nondairy animal proteins (poultry, meat, fish, eggs) along with low-alkali food might increase the risk of kidney stone recurrence, causing increased urine acidity, negative calcium balance, and decreased urine potassium, citrate, and magnesium excretion (58, 59). High animal protein content, regardless of being red meat and white meat, can result in a high purine load and increased uric acid load, both of which are associated with increased risk of kidney stones (10). A case-control study showed that persons who consumed greater quantities of red meat have a higher risk of kidney stones (60). In contrast, a case-control study in 1019 kidney stone patients and 987 healthy controls reported that meat and fish consumption had a negative association with the risk of kidney stones (61). Similarly, a cross-sectional study revealed that increased fish and meat score was correlated with lower rates of reported nephrolithiasis (62). A recent review showed that dietary meat intake through a decline in urine PH, citrate excretion, and increasing calciuria is a potential stone risk factor (10). Meanwhile, the ability of processed meats in developing kidney stones is higher due to their high sodium content that is directly correlated with urinary excretion of calcium and increased risk of nephrolithiasis (10, 63).

Dairy animal protein
We found a significant inverse association between dairy animal protein and risk of kidney stones. However, this association was not seen with whole-milk and skim-milk consumption. Higher consumption of dairy protein was associated with higher urinary calcium excretion and citrate but decreased uric acid and oxalate (20). These findings revealed a mixed effect of dairy protein intake on relevant lithogenic factors. The higher calcium excretion in the urine might be due to the effect of casein on intestinal absorption of calcium (64) and the higher calcium content in dairy products. Higher amounts of calcium can bind with oxalate in the intestine and decrease absorption

of oxalates (65). Greater intake of dietary calcium from nondairy or dairy sources is correlated with a decreased risk of kidney stones in previous cohorts (66). Furthermore, a systematic review and meta-analysis of observational studies did not find a significant association between milk consumption and kidney stone risk in their primary analysis as well as when stratified by whole milk or skim milk (67).

Limitations and strengths
A potential limitation of this review is related to the exposure assessment tool used in the included studies, as most studies used FFQs, which are prone to measurement error and recall bias. In addition, the observed associations may be affected by residual confounding factors that were not controlled for. Furthermore, several studies were unable to be included in the dose–response analysis due to insufficient data. Finally, further observational studies are needed as the number of eligible studies included in this review was low. However, this study has some strengths. Most of the included studies were high quality based on the Newcastle-Ottawa quality-assessment tool. All included publications used prospective cohorts, which may be less susceptible to recall and selection bias than other observational study designs and improve our understanding of the causal nature of this relation.

Conclusions
We found that a high intake of nondairy animal protein, total meat and meat products, red meat, and processed meat was associated with increased risk of kidney stones as well as a lower risk of kidney stones being associated with dairy consumption. There was no significant association between total protein, animal protein, poultry, fish, whole-milk, and skim-milk consumption and incidence of kidney stones. Given that most of the included studies have been reported from Western countries, extrapolating the results of these findings to other regions, especially Eastern countries, is premature and further observational studies are needed to address this.

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